79. (twice amended) A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes benzyloxy compounds and derivatives of benzyloxy compounds attached at position 5 of the indoxyl compounds to [alter the solubility, digestibility, color, and physical state] reduce the ability of the indoxyl compounds and the extra-cellular precipitate to move by diffusion or convective flow in the extracellular fluid.

80. (twice amended) A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes 5,5-bi-indoxyls attached at position 5 of the indoxyl compounds to [alter the solubility, digestibility, color, and physical state] reduce the ability of the indoxyl compounds and the extra-cellular precipitate to move by diffusion or convective flow in the extracellular fluid.

REMARKS

Reconsideration and allowance are respectfully requested.

Claims 69, 71, 72, 75, and 77-80 have been amended to provide a better definition of the invention. It is submitted that these amendments to the claims neither constitute new matter nor raise new issues and therefore should be entered.

The following are submissions, comments, and arguments in response to the numbered Sections of the Official Action mailed November 25, 1998 and the interview summaries of telephone interviews of the undersigned with the Examiner.

Section 3, page 2

It is submitted that the Brief Description of the Drawings on pages 14-16 is in complete compliance with 37 C.F.R. 1.74 and MPEP 608.01(f):

> 1.74 Reference to drawings
>
> When there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures and to the different parts by use of reference letters or numerals (preferably the latter).

Furthermore the detailed description of the invention beginning on page 17 of the specification completely conforms to the requirement of 37 C.F.R. 1.71 and MPEP 608.01 in that each reference numeral and each drawing is specifically and completely identified and described in the specification.

DECLARATIONS

Attached hereto are Declarations of Henry Rapoport, Ph.D. and Alan Epstein, MD., Ph.D., each under 35 U.S.C. 1.1132 traversing the grounds of rejection as identified by the Section numbers recited therein of the Official Action mailed November 25, 1998.

RESPONSE TO THE SECTIONS OF THE OFFICIAL ACTION

Action 5 (a'), page 3-4

> A review of the cited support reveals general teachings of the chemistry of indoxyl chemistry but does not provide either guidance on or exemplification of making or using the broadly claimed agents that would be therapeutic when administered *in vivo*. Further, the issue raised here is not only whether the making/using if soluble precipitable material is disclosed in the specification but also that the applicant has not taught how to make or use the instant invention, especially in view of Applicant's (page 15, section 21 of Paper No. 14) admission on the record that the therapeutic agent is "only therapeutic after it has been converted into an insoluble material because the therapeutic effect depends on the radiation field which is generated by the precipitate induced immobilization the isotope and its long term retention at the immobilized site." A review of the specification does not reveal the absolutely critical nature of radio-labeling of the therapeutic agent.

Response:

1. Making Soluble Precipitable Material

See the Declaration of Professor Rapoport.

Making indoxyls as the soluble precipitable material is found in the specification pages 20-23. Making the soluble precipitable material comprised of soluble and insoluble moiety specification pages 23 24. The method of radio labeling the therapeutic agent is described in the specification page 23 and in Figs. 15-17.

2. Using Soluble Precipitable Material

See the Declaration of Dr. Epstein.

The method and dosages of the bispecific reagent and the therapeutic agent in the present invention are readily taught by the prior art of ADEPT disclosed in the specification. In the present invention the therapeutic agent (the soluble precipitable material) and in the prior art of ADEPT, the prodrug, are both converted by the non-mammalian enzyme moiety of a previously bound bispecific reagent. In the present invention, the therapeutic agent which is a soluble precipitable material is enzymatically converted into an insoluble precipitate. In ADEPT, a soluble pro-drug is enzymatically converted into an active soluble drug.

It is widely known to those skilled in the art and published in the field that the immobilization of radio-isotopes can be used successfully for therapy. Examples have also been given in the specification of the invention on pages 7-8, 11. The immobilization of isotopes generates radiation fields that kill cancer cells in the immediate microregion of the deposited isotopes.

In accordance with the invention the "first therapeutic agent" (being a soluble precipitable material) is <u>not</u> therapeutic <u>per se</u> when administered in vivo. It only becomes therapeutic as disclosed in the specification when it is concentrated and retained <u>in situ</u>.

Action 5 (b'), 5(c'), 5(d'), page 4

A review of pages 9 and 10 reveals the disclosure of numerous references which report the enzymatic conversion of a pro-drug to an active drug in the extracellular space, however, none of the cited references have been submitted and therefore none of the references have been considered. However, it is noted that on page 10, paragraph 2, the specification clearly states that "ADEPT approach fails to successfully treat cancer", thus dosage and methods of administration used in the prior art would not be expected to enable the instant claims, further, it is noted that the cited references are to be found in the "Prior Art" section of the specification and that neither guidance on nor exemplification of administration or exemplification of or guidance for effective dosage are to be found in the portion of the specification drawn to the invention (c' and d'). As disclosed above the teachings on page 20-24 are drawn to indoxyl chemistry and no teaching or exemplification is provided for any of the other therapeutic reagents claimed and the argument is not found persuasive for the reasons disclosed in section (b') above.

Response:

See Declaration of Dr. Epstein.

Applicant has included a sample of the references for ADEPT cited in the specification of the application.

Although ADEPT fails to treat cancer successfully, the dose levels of the prodrug are relevant guidelines for dose levels for the therapeutic agent and the bispecific reagent in the present invention. ADEPT fails for reasons other than the administered dose of the prodrug-- most importantly because the active drug (which is produced by the enzymatic action of the enzyme moiety of the bispecific reagent converting a pro-drug into an active drug) diffuses away from its

site of production to enter the blood stream where it exerts a systemic toxic effect. The larger the tumor, the larger will be the number of production sites, the larger will be the number of active drug molecules which will diffuse into the blood to have a larger systemic toxicity.

However, in the present invention, the attack against the cancer is determined by the number of radio-isotope atoms which are immobilized, which is determined by the number of enzyme molecules which are bound (via the bound bispecific reagent) and the turn-over number of the enzyme ("turn-over number" is the number of molecules that can be converted from one state to another per unit time per molecule of enzyme).

See also Applicant response to (a') above.

Action 5 (e'), page 4

> The argument is drawn to the bispecific reagent, however, as clearly repeated on page 8 of the response, the issue raised here is that the therapeutic agents may be inactivated *in vivo* and because the applicant did not distinctly and specifically point out the supposed errors rejection, the rejection is maintained.

Response:

The therapeutic agent is not a protein and proteolytic degradation is, therefore, not relevant. The therapeutic agent is a radio-labeled soluble precipitable material. It circulates freely in all body fluid which of course includes, as recited in the Official Action "fluids, cells and tissues." Since the therapeutic agent is only converted into an insoluble material by the non-mammalian enzyme moiety of the bound bispecific reagent, this is the only location where it will be immobilized and be retained for a long time, and, therefore, this will be the only location where it will generate

radiation fields (which destroy all cancer cells in the immediate microregion surrounding each location of the bound non-mammalian enzyme) and be therapeutic effect. The agent is only therapeutic after it has been converted into an insoluble material because only when immobilized does a sufficiently large number of radioactive isotopes become deposited and be retained. In all other locations it may exert a minor injury and toxicity (because it is radio-labeled) but the radiation dose is not sufficient to produce a therapeutic effect. Immunological inactivation is not foreseen because the administration of the therapeutic agent will be the first time the host has been exposed to the novel agent.

Action 5(f'), pages 4, 5

> Although the word "adapted" has indeed been replaced in the recited claims, the argument drawn to dosage and methods of administration is not found persuasive for the reasons set forth in section (b') above.

Response:

See Applicant response to 5(b'), 5(c'), and 5(d') above.

Action 5(g'), page 5

> As recited in claim 69, the term therapeutic agent includes peptides, carbohydrates, chitosan, chitin, proteoglycans and synthetic polymers as well as indoxyl compounds and contrary to applicant's arguments, peptides, which read on proteins, and proteoglycans are claimed." Claim 69 specifically claims that the therapeutic agent (as defined by the claim) is converted into a extracellular precipitate which the claim defines as an insoluble and non-digestible precipitate and further Applicant admits on the record that the specification does not describe proteins and peptides as candidates for the soluble precipitable material. (h') the argument is not persuasive for the reasons previously disclosed in section (a') and (c') above.

Response:

The original claims are part of the disclosure of the application: in re Meyers (CCPA 1969) 410F2d 420, 161 USPQ 668, and the disclosure can be amended to conform with the claims. Ex parte Wilson et al (POBA 1957) 116 USPQ 595. See MPEP in 608.1(1), 608.4, 706.03(o), 2163.06, 2163.06, "III"

In response to the allegation that the specification does not describe proteins and peptides as candidates for the soluble precipitable material, applicant submits that original claim 5 recites:

> "... in which the first therapeutic agent is a soluble agent and is an organic chemical comprising at least one of peptides, including opio-melanins, of carbohydrates including cellulose, chitosan, and chitin, and of proteoglycans, of synthetic polymers, and of indoxyl compounds having molecular positions 1-7"

Action 5(h'), page 5

The argument is not persuasive for the reasons previously disclosed in section (a') and (c') above.

Response:

See Applicant response 5(a') and 5(c') above.

Action 5(I'), page 5

Applicant's stated opinion is noted but it is clear that one of skill in the art would expect that an insoluble precipitate would be removed from the claimed region either by convection, diffusion, or by phagocytosis. Applicant is invited to submit objective evidence demonstrating that the insoluble precipitate will not diffuse away, move away or be removed from the area by phagocytosis. As drawn to tethering of the precipitate, applicant is arguing limitation not recited in the claims as presently constituted. It is noted that amendment of the claims to recite tethering limitations in an amendment submitted after final would raise a new issue, not previously considered, and that the amendment would not be entered for this reason.

Response:

See Declaration of Dr. Epstein.

In the proposed invention, the product of the enzymatic conversion is insoluble and stable. Insoluble materials do not diffuse-- only soluble materials diffuse. In the present invention, the insoluble precipitate is not removed from the area by convective flow because tumors lack effective lymphatic drainage (see references in specification page 35-36). Further, in the present invention, the insoluble precipitate is not removed from the area by phagocytic activity because macrophage and phagocytic activity in the tumor is reduced (see references in specification page 35-36).

For example, trypan blue adsorbed to albumin (a soluble macromolecule) is retained in tumor tissue for over 5 days, whereas it only remains in normal tissue for a few hours--this difference reflects the fact that normal tissues, but not cancer tissues have an effective lymphatic drainage. Those skilled in the art would understand that this difference (hours in normal tissues and days in cancer tissue) would be amplified for insoluble materials. This is confirmed by the long term retention of insoluble DNA which has been relocated from inside cells to the extra-cellular fluid.

Ultimately, the insoluble precipitate will be removed by convection and phagocytosis. However, in accordance with the present invention, such removal from tumor tissue will be slower than from normal tissues. This difference is a "window of opportunity" for the therapist.

Action 6(a'), page 6

because the issue raised here is not whether the instant invention circumvents problems related to impermeability of tumors to antibodies and lack of uniform distribution of antibodies, but rather whether the instant specification is enabling. For the reasons stated, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Response:

See Applicant response 5(b'), 5(c'), 5(d') above.

Action 6(b'), page 6

... for the reasons previously disclosed in section 5(b') above.

Response:

See Applicant response 6(a') above.

Action 6(c'), page 6

a review of the cited pages reveals support for the advantage of a therapeutic agent to be made cell impermeant (p. 19) but no discussion drawn to making soluble precipitable material into a cell impermeant molecule on pages 22 and 29-30.

Response:

The specification refers to making the soluble precipitable material cell impermeant on page 19 "the first therapeutic agent can be made cell impermeant by attaching one of a number of cell impermeant molecules at least including peptides or polymers having a molecular size greater than 1,000 Daltons and anionic chemicals including thiols."

See also Applicant response to Action item 8 below.

Action 7, page 6

Applicant argues that making the soluble precipitable material into a cell impermeant molecule is described at pages 19, 22 and 29-30 of the specification. The argument has been noted but has not been found persuasive.

Response:

See Applicant response to Action item 8 below.

Action 8, pages 6, 7

Applicant argues that making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 22 and 29 30. The recitation of materials having a molecular weight of greater than 1000 Daltons defines a large molecule and thereby a cell impermeant chemical. The argument has been noted, but has not been found persuasive. Further the issue raised here was not the definition of a large molecule that is cell impermeant but rather the issue raised was how to use a large molecule, as broadly claimed, that will function as claimed.

Response:

See Declaration of Professor Rapoport and Declaration of Dr. Epstein.

Action 9, Section (6e), page 7

Applicant argues that, as drawn to the rejection 6(e) that the therapeutic agent is radio-labeled. The argument has been noted but has not been found persuasive as drawn to claims 69-82 because radio labeling is only claimed in claim 83 which is dependent upon claim 69.

Response:

The first therapeutic agent is radioactive and, therefore, must cause some cell damage to cancer cells and all normal systemic cells while it is soluble and circulating in the body fluids. This cell damage does not therapeutic because the concentration of the radio-active molecule in the body

fluid is low and because it does not remain in the body fluids for a long time. When the soluble first therapeutic agent is converted into an insoluble material the concentration of the radio-active molecule in the precipitate is high and also because it is retained in situ for a very long time. The combined effect of high concentration and long term retention is to generate an intense radiation field that destroys cancer cells and is, thus, therapeutic after its conversion to the insoluble and non-digestible precipitate.

Action 9, Section 6(f), page 7

> Applicant argues that, as drawn to the rejection 6(f) that as drawn to "disposed" the precipitate is formed by the catalytic action of the non-mammalian enzyme. The argument has been noted but has not been found persuasive because the term "disposed" has not been defined by either the claim or the specification.

Response:

Applicant has amended Claim 69 to provide a better definition of the invention.

Action 9, Section 6(I), page 7

Applicant argues that, as drawn to rejection 6(I) that the markush grouping is proper because the members of the group possess a property in common. The argument has been noted but is not persuasive because it is not clear whether the peptides and carbohydrates claimed are limited to those recited in the claim or whether they include other moieties of the same class.

Response:

Since a Markush group by definition defines a constructed group of constituents the Applicant is entitled to equivalence of said group.

Action 9, Section 6(I), page 8

The argument has been noted but has not been found persuasive a review of the cited pages reveals support for the advantage of a therapeutic agent to be made cell impermeant (p.19) but no discussion drawn to making soluble precipitable material into a cell impermeant molecules on pages 22 and 29-30 and does not define the claimed materials and further the recitation of weight of greater than 1000 Daltons does not define the metes and bounds of the claimed invention.

Response:

The specifications referring to making the soluble precipitable material cell impermeant is found on page 19 (not pages 22, 29-30).

See also Applicant response to Action item 8.

Action 9, Section 6(s), page 8

The argument has been noted but has not been found persuasive because although the claim has been amended to recite the effects of altering indoxyl compounds, the claim has not been amended to define derivatives of benzyloxy compounds.

Response:

Claim 79 has been amended by the Applicant to provide a better definition of the invention.

Action 10, page 8

The argument has been noted but has not been found persuasive because of the broadly recited prodrugs in WO 91/109134. Applicant is invited to submit objective evidence to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product, particularly as drawn to the anti-cancer drugs recited on page 9, line 14 through page 11.

Response:

See Declaration of Dr. Epstein.

Action 9, page 9

Objections to previously amended claim 69.

Response:

Claim 69 amended in view of Section 9 is submitted herein.

Action 11, pages 9, 10

The limitation of "at least several days" in claim 69 and the limitation of "alter solubility, digestibility, color and physical state" in claims 78-80 have no clear support in the specification and the claims as originally filed.

Response:

Claim 69 has been amended to provide a better definition of the invention.

Claims 78-80 have been amended to provide a better definition of the invention.

PUBLICATION EXHIBITS

Attached hereto are Exhibits A-J which are copies of papers in technical publications which bear out the state of the art of the background of the claimed subject matter of the invention of the application and thereby set forth the understanding of one skilled in the art relevant to the claimed invention at the time of the filing of the above-identified application.

A. References to ADEPT, Pages 1 and 2

B. Lymphatic drainage from the extracellular fluid of tumor tissue is impaired (leading to accumulation of macromolecules in this location), page 3

C. Macrophages are inhibited in tumor, page 4

D. Construction and Characterization of a Fusion Protein of Single Chain Anti-CD20 Antibody and Human β-Glucuronidase for Antibody-Directed Enzyme Prodrug Therapy. Blood, Vol. 92, No 1 (July 1), 1998: pp 184-190

E. Toward Antibody-directed Enzyme Prodrug Therapy with the T268G Mutant of Human Carboxypeptidase A1 and Novel *in Vivo* Stable Prodrugs of Methotrexate. The Journal of Biological Chemistry, Vol. 272, No 25, June 20, 1997 pp 15804-15816

F. Use of conjugates of bovine serum albumin with poly(alkylene oxide)s for solubilization of riboflavin ester[1] Biotechnol, Appl. Biochem. 17, 337-348 [1993]

G. The bioactivation of CB 1954 and its use as a prodrug in antibody-directed enzyme prodrug therapy (ADEPT) Cancer and Metastasis Reviews 12: 195-212, 1993

H. Construction, Expression, and Activities of L49-sFv-β- Lactamase, Single-Chain Antibody Fusion Protein for Anticancer Prodrug Activation Bioconjugate Chem. 1997, 8, 510-519

I. Preparation and Characterization of a β-Lactamase-Fab' Conjugate for the Site-Specific Activation of Oncolytic Agent Bioconjugate Chem. 1992, 3, 42-48

J. Enhancement of the *in Vivo* Activities of Phosphorylated Mitomyin C and Etoposide Derivatives by Monoclonal Antibody-Alkaline Phosphatase Conjugates [Cancer Research 49, 5789-5792, November 1, 1989]

Exhibit A-E are particularly relevant to Dr. Epstein's Declaration enclosed herewith.

Exhibit F is particularly relevant to Dr. Rapoport's Declaration enclosed herewith.

Exhibits G-J are particularly relevant to the prodrug therapy ADEPT referred to in the specification of the above-identified application.

SUMMARY

It is submitted that the formal objections to claims 69-83 have been overcome by the amendments to the claim herein.

It is further submitted that claims 69-83 have been patentably distinguished over the reference (International Application Number WO 91/09134) which does not teach or suggest that the therapeutic reagents are adapted to be converted into insoluble non-digestible precipitates as set forth in claims 69-83.

Therefore, it is submitted that claims 69-83 should now be found to be in condition for allowance

Favorable action is solicited.

Respectfully submitted,

Dated: May 25, 1999

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